Critical Care Nephrology and Acute Kidney Injury

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Medication Management in the Critically Ill Patient with Acute Kidney Injury

Michael L. Behal,[1,2] *Alexander H. Flannery*[1,2] *and Erin F. Barreto*[3]

Abstract

AKI occurs frequently in critically ill patients. Patients with AKI, including those who require KRT, experience multiple pharmacokinetic and pharmacodynamic perturbations that dynamically influence medication effectiveness and safety. Patients with AKI may experience both subtherapeutic drug concentrations, which lead to ineffective therapy, and supratherapeutic drug concentrations, which increase the risk for toxicity. In critically ill patients with AKI not requiring KRT, conventional GFR estimation equations, especially those based on serum creatinine, have several limitations that can limit the accuracy when used for medication dosing. Alternative methods to estimate kidney function may be informative, including use of measured urinary creatinine clearance, kinetic eGFR, and equations that integrate novel kidney biomarkers. For critically ill patients with AKI requiring KRT, physicochemical properties of the drug, the KRT prescription and circuit configuration, and patient-specific factors each contribute to medication clearance. Evidence-based guidance for medication dosing during AKI requiring KRT is often limited. A working knowledge of the basic tenets of drug elimination during KRT can provide a framework for how to approach decision making when the literature is lacking. Iterative re-evaluation of a patient's progress toward therapeutic goals with a medication must occur over the arc of critical illness, including and especially in the setting of dynamic kidney function.

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[1]Department of Pharmacy Practice and Science, University of Kentucky College of Pharmacy, Lexington, Kentucky
[2]Department of Pharmacy Services, University of Kentucky HealthCare, Lexington, Kentucky
[3]Department of Pharmacy, Mayo Clinic, Rochester, Minnesota

Correspondence: Dr. Erin F. Barreto, Department of Pharmacy, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905. Email: Barreto.erin@mayo.edu

Introduction

AKI occurs in 30%–60% of critically ill patients and worsens morbidity and mortality.[1] Dynamic kidney function in critical illness complicates safe and effective medication use. Nearly 25% of the most prescribed medications in intensive care units (ICUs) have the potential to cause AKI.[2,3] Nephrotoxin stewardship is necessary to prevent and ameliorate adverse drug events, avoid or limit incident nephrotoxic AKI and related sequelae, and promote optimal resource utilization.[4] We refer the reader to the detailed characterization of drug-induced AKI previously published in *CJASN's* Critical Care Nephrology and Acute Kidney Injury series for additional details.[3] In addition to nephrotoxins, an estimated 60% of medications used in the hospital setting are cleared by the kidney,[5] thus potentially warranting dose adjustments in patients with AKI.[6–10] Appropriate dosing of medications in AKI must balance the competing risks of underdosing, which could jeopardize treatment effectiveness, with overdosing, which could lead to medication-related toxicity. This review will discuss drug pharmacokinetics and present clinical examples and approaches to medication management in patients with AKI, including those receiving KRT. The use of KRT for management of intoxications or poisonings has been carefully summarized elsewhere[6] to which we refer the reader.

Influence of the Kidney on Drug Pharmacokinetics

Kidney dysfunction significantly influences drug pharmacokinetics. Patients with AKI typically present with an expanded volume of drug distribution, which reduces circulating concentrations of hydrophilic molecules.[7] Acid-base abnormalities and accumulation of uremic toxins in kidney dysfunction may alter protein binding and cytochrome P450 enzymatic activity.[8] These pharmacokinetic changes in protein binding and metabolism have been demonstrated in CKD, but their clinical relevance in AKI is less well understood.

The most consequential pharmacokinetic attribute affected by AKI is drug elimination. Kidney clearance of a medication is the net effect of glomerular filtration, tubular secretion, and, to a lesser extent, reabsorption. Although the primary method used clinically to approximate kidney clearance of a medication is the eGFR or estimated creatinine clearance, these may not reflect actual kidney clearance of medications, particularly in dynamic conditions.[9] Only free or unbound molecules are excreted by glomerular filtration, which constitutes approximately 20% of kidney plasma flow.[10] Medication clearance through filtration may therefore not be linearly affected by hypoperfusion due to the relatively limited degree of flow directed at this pathway. The remaining 80% of kidney plasma flow is directed at

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peritubular capillaries, which facilitate tubular secretion including of protein-bound medications.[10–12] In the setting of compromised kidney blood flow, medications highly reliant on active tubular secretion, such as metformin, dabigatran, and foscarnet, may exhibit altered clearance compared with the predicted elimination based on eGFR.[10,11] Finally, reabsorption of certain drugs from the glomerular filtrate can occur in the proximal and distal tubules.[12] Reabsorption is governed by urine flow rates, pH, and in some cases (*e.g.*, lithium[13]) electrolyte and fluid status, all of which can be altered in AKI. The clinical impact of altered reabsorption on medication handling is not well understood.

Decreased medication clearance in AKI may lead to accumulation of both the parent drug and renally eliminated metabolites. Delayed metabolism due to acute or chronic end-organ dysfunction may lead to a prolonged exposure to these pharmacologically active metabolites. For example, morphine undergoes metabolism in the liver producing morphine-3- and 6-glucuronide. Morphine-6-glucuronide is a pharmacologically active metabolite, and its clearance is dependent on kidney elimination.[14] Failure to account for lower kidney clearance in the setting of AKI would result in accumulation of the active metabolite and higher risk for opioid toxicity. Similarly, although midazolam is primarily eliminated hepatically, the major metabolite 1-hydroxy-midazolam is pharmacologically active and 45%–75% eliminated renally, thus risking accumulation and oversedation in critically ill patients with AKI.[15]

Medication Management in AKI without KRT

Traditional Approach for Assessing Kidney Function in the Critically Ill

The historical strategy for quantifying kidney function for drug dosing was based on the estimated creatinine clearance using the Cockcroft–Gault equation. In draft guidance published in 2010, the US Food and Drug Administration recommended either the estimated creatinine clearance or the eGFR expressed in ml/min (based on the Modification of Diet in Renal Disease equation multiplied by the patient's body surface area and divided by 1.73) for kidney function assessment in pharmacokinetic studies.[16] Since then, a greater proportion of new drug labels have included Modification of Diet in Renal Disease–based dosing thresholds (17% in 2015 to 47% in 2017).[17] An update in 2020 endorsed use of the 2012 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR equation expressed in ml/min as well,[18,19] and it is likely that future iterations will include the more recent raceless eGFR equations.[20] Regardless of the equation used, most renally eliminated medications used in the critically ill are conventionally dosed according to creatinine-based GFR thresholds.

Creatinine has substantial limitations as a kidney biomarker in the critically ill. As the terminal byproduct of skeletal muscle metabolism, nonrenal factors such as altered body composition, deconditioning, skeletal muscle catabolism, and certain disease states including cirrhosis and malnutrition alter creatinine production independent of GFR.[21] This issue is exemplified by an ICU patient with paraplegia maintained on outpatient mechanical ventilation who presents with pneumonia and a serum creatinine of 0.4 mg/dl despite oliguria. Moreover, creatinine exhibits a 48–72-hour lag time from the onset of kidney injury before changes in the serum concentration are observed. The so-called "creatinine-blind" period resulting from this lag increases the risk of medication overdosing during the evolution of AKI and medication underdosing during recovery (Figure 1). Finally, although most of the creatinine produced is eliminated through glomerular filtration, approximately 10% undergoes proximal tubular secretion. The degree to which creatinine is secreted is much higher in individuals with a reduced GFR.[22] Interactions between drugs and creatinine at tubular transporters (*e.g.*, organic cation transporter 2, organic anion transporter 1, organic anion transporter 3) can lead to higher serum creatinine concentrations independent of underlying kidney function.

Sulfamethoxazole/trimethoprim, which is both renally eliminated and nephrotoxic, is subject to this issue because trimethoprim is a potent organic cation transporter 2 inhibitor.[10] In cases where a serum creatinine rise is observed after sulfamethoxazole/trimethoprim exposure, it is challenging to differentiate true nephrotoxicity from pseudonephrotoxicity.[23] Observed rises in serum creatinine after exposure to piperacillin/tazobactam in combination with vancomycin may also be attributable, at least in part, to interactions with creatinine at tubular transporters.[24] A framework has been proposed to include novel kidney biomarkers in the evaluation of nephrotoxic AKI that may differentiate true nephrotoxicity from pseudonephrotoxicity.[24–26] The strategy uses a 2×2 table, which simultaneously considers functional (±) and injury (±) biomarkers to classify patients into one of four categories: no dysfunction/no injury, injury without dysfunction (some have referred to this as subclinical AKI), dysfunction without injury, and dysfunction/injury. Pseudonephrotoxicity is one explanation for a change in creatinine without corresponding evidence of injury (dysfunction without injury).

Alternative Methods for Kidney Assessment for Drug Dosing in AKI

Measured Clearance

Creatinine clearance can be directly measured using timed urine collections (Table 1) or by elimination of a freely filtered biologically inert exogenous compound such as inulin, iohexol, or iothalamate.[21] These tools are rarely performed clinically for medication dosing in critically ill patients because of the technical complexity, duration of time required to sample and analyze the data, and expense. Newer technology involving noninvasive or minimally invasive real-time, continuous GFR monitoring based on clearance of fluorescent compounds holds promise for critically ill patients receiving renally eliminated medications.[27] Although not yet commercially available, this technology would allow clinicians to detect in near real time rapidly changing kidney function to adjust medication doses. Any future implementation of such a tool will face practical issues relevant to this clinical scenario—which patients and which medications should be the focus, with what frequency is dose

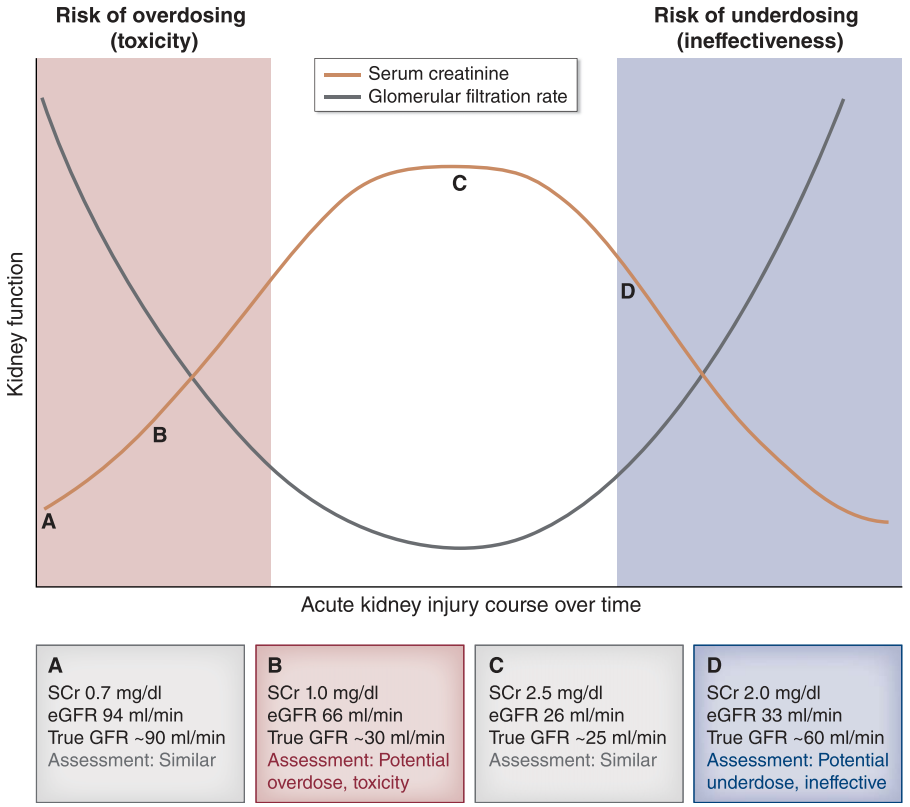

Figure 1. Impact of dynamic AKI course on medication dosing in the critically ill. Early in the course of acute illness, serum creatinine is a reasonable approximation of kidney function (as indicated at timepoint A). As a patient's kidney function deteriorates, underlying loss of true GFR precedes an observed rise in serum creatinine by up to 48 hours (as indicated by the red shaded box). This has been referred to as the creatinine-blind period. During this interval, there is a risk for overdosing narrow therapeutic window medications and increasing the risk for systemic toxicity (kidney or nonkidney). An example would be undetected loss of kidney function resulting in vancomycin accumulation (indicated by example discrepant parameters in B). Once serum creatinine has plateaued and kidney function stabilizes, it provides a reasonable approximation of the deteriorated kidney function for drug dosing (as indicated at timepoint C). As a patient's kidney function recovers, the underlying true GFR improves before serum creatinine normalizes (as indicated by the blue shaded box). During this interval, patients are at risk for medication underdosing and a lack of effective therapy. As an example, if the dose of levetiracetam is not increased commensurate with the patient's improving underlying kidney function, breakthrough seizures may occur (indicated by example discrepant parameters in D). SCr, serum creatinine.

manipulation both high yield and practical, and what is the cost-effectiveness of such an approach. These tools also reflect glomerular filtration only; thus, renal clearance of medications mediated by tubular transporters will not be captured.[28]

Kinetic eGFR

The traditional creatinine-based equations for GFR estimation (*e.g.*, Cockcroft–Gault estimated creatinine clearance, CKD-EPI eGFR equation) are designed for use at steady state, a scenario far divorced from the critically ill patient with AKI. As an example, an eGFR of 40 ml/min provides little actionable information about drug elimination in an ICU patient with anuria. More appropriate dosing in this circumstance would approximate an eGFR <10 ml/min. Other creatinine-based equations have been developed for use in unstable kidney function. The kinetic estimated GFR (KeGFR) is the most recent equation of this type that considers the trajectory of creatinine change rather than a single static point estimate[29] (Table 1). In a cohort of critically ill patients with AKI, use of the KeGFR versus estimated creatinine clearance or CKD-EPI eGFR resulted in medication dosing discordance in approximately one third of cases.[30] A pharmacokinetic study found the KeGFR best predicted vancomycin clearance in patients with unstable kidney function compared with several other commonly used equations including estimated creatinine clearance and CKD-EPI eGFR.[31]

Novel Kidney Biomarkers

To improve on the limitations of creatinine as a tool to guide medication management, adjunct or alternative biomarkers have been proposed to better characterize kidney function (*e.g.*, cystatin C or proenkephalin), stress (*e.g.*, tissue inhibitor metalloproteinase 2 insulin growth factor binding protein 7), or damage (*e.g.*, neutrophil gelatinase–associated lipocalin, kidney injury molecule 1).[25,26]

For dosing renally eliminated medications, among these new tools, novel functional biomarkers are of greatest relevance. Cystatin C, for example, is an endogenous, low molecular weight protein derived from all nucleated cells, freely filtered at the glomerulus, and reabsorbed and metabolized in the proximal tubule.[32] The results from a

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Table 1. Select kidney clearance equations used during AKI with and without KRT

Clearance Assessment	Equation	Variables
AKI without KRT		
Measured urinary creatinine clearance[21]	$(U \times V)/P$	U=urinary concentration of creatinine V=urinary flow rate (volume per unit time) P=plasma concentration of creatinine during the urine collection period
Kinetic eGFR[29,a]	$\left[\frac{CrCl_{ss} \times [PCr]_{ss}}{[PCr]_{mean}}\right] \times \left[1 - \left(\frac{24 \times \Delta PCr}{\Delta Time \times \left(\frac{MaxPCr}{day}\right)}\right)\right]$	$[PCr]_{ss}$=steady-state plasma creatinine concentration[b] CrCl=creatinine clearance at steady state[b] $[PCr]_{mean}$=average of two creatinine values used in the kinetic evaluation that are <48–72 h apart ΔPCr=change in plasma creatinine between two assessments (*i.e.*, $PCr_{end} - PCr_{start}$) ΔTime=interval in hours between the two plasma creatinine assessments MaxΔPCr/day=maximal change in plasma creatinine per day that can occur if kidney function is completely lost, ideally determined using patient-specific data, but otherwise 1.5 mg/dl per day can be used as an approximation for most adult patients
2012 CKD-EPI $eGFR_{cysC}$ (ml/min per 1.73 m^2)[19]	$\left[133 \times \left[\min\left(\frac{S_{Cys}}{0.8}, 1\right)^{-0.499}\right] \times \left[\max\left(\frac{S_{Cys}}{0.8,1}\right)^{-1.328}\right] \times 0.996^{Age} \times [0.932 \text{ if female}]\right]$	min (S_{Cys}/0.8, 1)=indicates the minimum of S_{Cys}/0.8 or 1 max (S_{Cys}/0.8, 1)=indicates the maximum of S_{Cys}/0.8 or 1 To re-express the results in ml/min as has been recommended for drug dosing, multiply the result by (body surface area/1.73 m^2)
2021 CKD-EPI $eGFR_{cr\text{-}cysC}$ (ml/min per 1.73 m^2)[20]	$\left[135 \times \left[\min\left(\frac{S_{Cr}}{K}, 1\right)^{a}\right] \times \left[\max\left(\frac{S_{Cr}}{K}, 1\right)^{-0.544}\right] \times \left[\min\left(\frac{S_{Cys}}{0.8}, 1\right)^{-0.323}\right] \times \left[\max\left(\frac{S_{Cys}}{0.8}, 1\right)^{-0.778}\right] \times 0.9961^{Age} \times [0.963 \text{ if female}]\right]$	K=0.7 for female patients, 0.9 for male patients min (S_{cr}/K, 1)=indicates the minimum of S_{cr}/K or 1 max (S_{cr}/0.8, 1)=indicates the maximum of S_{cr}/0.8 or 1 a=−0.219 for female patients, −0.144 for male patients min (S_{Cys}/0.8, 1)=indicates the minimum of S_{Cys}/0.8 or 1 max (S_{Cys}/0.8, 1)=indicates the maximum of S_{Cys}/0.8 or 1 To re-express the results in ml/min as has been recommended for drug dosing, multiply the result by (body surface area/1.73 m^2)
AKI with KRT[c]		
CVVH *Clearance (predilution replacement fluids)*[41]	$Q_{UF} \times SC \times \left[\frac{Q_b}{Q_b + Q_{rf}}\right]$	Q_{UF}=ultrafiltration flow rate SC=sieving coefficient Q_b=blood flow rate Q_{rf}=predilution replacement fluid flow rate
CVVH *Clearance (postdilution replacement fluids)*[41]	$Q_{UF} \times SC$	Q_{UF}=ultrafiltration flow rate SC=sieving coefficient
CVVHD *Clearance*[41]	$Q_d \times SA$	Q_d=dialysate flow rate SA=saturation coefficient
CVVHDF *Clearance*[41]	$(Q_{UF} + Q_d) \times SA$	Q_{UF}=ultrafiltration flow rate Q_d=dialysate flow rate SA=saturation coefficient

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; KeGFR, kinetic estimated GFR.

[a]A revised KeGFR equation with cystatin C has been proposed[37] but not empirically evaluated for medication dosing. The primary difference is in the calculation of the $(\frac{MaxΔPCysC}{day})$ aspect of the denominator, which aims to account for the maximal change in plasma cystatin C that can occur over the day if kidney function is completely lost. To make this calculation with cystatin C, one uses the [([PCysC]$_{ss}$×eGFR)/[PCysC]mean]×(1.44/Vd) where Vd represents the volume of distribution of cystatin C, which is estimated at 0.2×body weight.

[b]$CrCl_{ss} \times [Cr]_{ss}$ reflect steady-state creatinine production rate, analogous to the U×V in the clearance equation. Calculation of $CrCl_{ss} \times [Cr]_{ss}$ can be performed once and used throughout the AKI event.

[c]Clearances listed represent only the KRT component of clearance, which is one component of total body clearance of a medication (renal, nonrenal, KRT). Other sources of drug clearance, including residual kidney function, must be simultaneously considered when estimating doses.

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systematic review suggested eGFR estimated with cystatin C improves the prediction of drug concentrations and drug clearance compared with eGFR derived from creatinine. Most of the published literature uses cystatin C to predict antibiotic clearance, but other drug classes including cardiovascular medications and antineoplastics have been studied.[33] Although cystatin C has not been well validated for prediction of measured GFR in the critical care setting, these data demonstrate the promise for prediction of drug clearance, an alternative and highly relevant end point. In the critical care setting, however, nonrenal determinants of cystatin C, including obesity, malignancy, inflammatory states, high-dose corticosteroid exposure, and solid organ transplantation, are prevalent and must be considered when interpreting observed concentrations.[32] Still, incorporation of the $eGFR_{cystatinC}$ or the $eGFR_{creatinine\text{-}cystatinC}$ in a structured dosing model used in the critically ill improved pharmacokinetic target attainment for vancomycin in patients with stable kidney function.[34,35] In AKI, cystatin C changes are detected more rapidly than changes in serum creatinine.[36] Similar to creatinine-based eGFR equations, cystatin C–based equations are subject to the same limitations in non–steady-state conditions. Serial monitoring could detect kidney deterioration or recovery sooner, and cystatin C could be incorporated into a revised KeGFR equation.[37] We are not aware of empirical data that assess these alternative potential applications for cystatin C to guide medication management. Proenkephalin is another novel functional biomarker that outperforms creatinine-based approaches to determining GFR, particularly in non–steady-state conditions, although data relating proenkephalin to medication dosing are scarce.[38]

Medication Management in AKI with KRT

Progression of AKI will require initiation of KRT in up to 5% of all cases and a much greater proportion in the critically ill.[39] Physicochemical properties of the medication, the KRT prescription and circuit configuration, and patient-specific factors each contribute to the impact of KRT on medication clearance[40,41] (Table 2). The ability of a medication (or any other solute) to pass through the semipermeable dialyzer membrane is referred to as the sieving coefficient for convective clearance and the saturation coefficient for diffusive clearance. The sieving coefficient and saturation coefficient range from 0 to 1, where 0 represents no movement across the membrane and 1 is free movement. The sieving coefficient and saturation coefficient are best determined from the primary literature or patient-specific values calculated from the ratio of medication concentration in the ultrafiltrate (convective clearance) or effluent (diffusive clearance) to the concentration in the plasma. When otherwise unavailable, the sieving coefficient and saturation coefficient can be approximated by the formula (1 − fraction of medication bound to plasma protein) because only unbound medications are cleared by the KRT circuit. Fraction unbound can be obtained from the primary literature or medication package inserts, both of which have been shown to reasonably correlate with sieving coefficient.[42] This estimating strategy should only be used when other information is unavailable because it oversimplifies the numerous factors that affect a medication's KRT clearance. The impact of these medication properties on KRT clearance, including molecular weight, protein binding, volume of distribution, and water solubility, are summarized in Table 2. A prototype of a highly cleared medication would include high kidney clearance, low volume of distribution, low molecular weight, and low degree of protein binding.

Circuit configuration will also influence KRT drug clearance.[40] Intermittent KRT modalities (*e.g.*, intermittent hemodialysis over 3–4 hours) contribute greater clearance per unit time than continuous KRT (CKRT), which delivers support over a 24-hour interval. Convective clearance modalities (*e.g.*, continuous venovenous hemofiltration) clear middle molecular weight solutes to a greater degree than diffusive clearance modalities (*e.g.*, continuous venovenous hemodialysis). Still, in a diffusive clearance circuit, there may be a degree of unmeasured filtration and backfiltration across the membrane that allows for middle molecular weight molecule passage. Greater KRT intensity (*i.e.*, higher KRT dose) is also associated with greater medication clearance.[43] This is one reason why slow continuous ultrafiltration primarily affects fluid and only limitedly contributes to medication clearance. Site of replacement fluids used in convective CKRT modalities could affect degree of medication clearance. Predilution replacement dilutes blood entering the circuit, thereby modestly decreasing solute concentrations and medication clearance. In a postdilution configuration, the concentration entering the circuit is higher, thereby resulting in relatively greater medication clearance. KRT efficiency may also be influenced by dialyzer composition and lifespan.[44] Circuit downtime and interruptions can be common and will affect delivered KRT dose. CKRT circuits are down a median (interquartile range) 3 (1–8) h/d or what amounts to 8%–28% of total treatment time.[45] The impact of circuit downtime in intermittent modalities is not well characterized but overall expected to be less consequential because there are natural on and off periods throughout the day. Prolonged circuit downtime that is not accounted for will decrease medication clearance, and doses may need to be adjusted downward. No specific recommendations regarding medication dosing around circuit downtime are available; however, a practical approach involves re-evaluation of medication doses if a circuit is down for more than 4–6 consecutive hours in a 24-hour period. Clinicians should be especially cognizant of circuit downtime when a patient is using a narrow therapeutic window medication. As an example, dosing of bivalirudin, a parenteral direct thrombin inhibitor with moderate kidney elimination, would need to be re-evaluated in the presence of significant KRT downtime and more frequent laboratory monitoring may be required.

Finally, in addition to physicochemical properties of the medication and KRT configuration considerations, several patient-specific factors must also be considered. The type of vascular access used for KRT can affect blood flow rates through the dialyzer and medication clearance.[46] In addition, patients who receive acute KRT may have modest residual kidney function. More than 0.5 ml/kg per hour urine output during KRT may signal clinically significant kidney clearance over and above KRT. Serum

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Table 2. Summary of factors associated with clearance during AKI requiring KRT

Factor	Impact and Considerations
Physicochemical properties of the medication[a]	
Molecular weight	Medication molecular weights are generally classified as low (<1000 Da), middle (1000–30,000 Da), or high (>30,000 Da). Lower molecular weight medications exhibit greater clearance during KRT. Example of low molecular weight medication (*i.e.*, highly cleared): levetiracetam (170 daltons) Example of middle molecular weight medication: vancomycin (1450 daltons) Example of high molecular weight medication (*i.e.*, minimally cleared): rituximab (145,000 daltons)
Protein binding	Albumin and α-1 acid glycoprotein are high molecular weight proteins (64,000 and 44,000 Da, respectively), which can attach to circulating drug. Only unbound (free) drug is cleared through KRT. Medications with high protein binding (>80%–90%) exhibit lower clearance during KRT. Example of highly protein-bound medications (*i.e.*, minimally cleared): valproic acid, phenytoin, warfarin
Volume of distribution	KRT clears the intravascular space; thus, medications with a lower volume of distribution (*e.g.*, <1 L/kg) are more likely to be cleared. Use of CKRT may allow for ongoing drug redistribution from the peripheral compartment (*i.e.*, tissue) to the central compartment (*i.e.*, plasma) that could contribute to increased clearance over time. Example of low volume of distribution medications (*i.e.*, highly cleared): gentamicin (0.25–0.35 L/kg), lithium (0.7–1 L/kg) Example of high volume of distribution medication (*i.e.*, minimally cleared): digoxin (7 L/kg), propofol (60 L/kg)
Circuit configuration	
Modality (intermittent, continuous)	Intermittent KRT is associated with on and off dialysis intervals, whereas CKRT is over 24 h. All else equal, clearance per unit time will be higher with intermittent KRT. Where possible, medication doses should be administered after intermittent KRT sessions or supplements may be given to account for potentiated clearance. Changing modalities should prompt re-evaluation of the medication dosing schema.
Solute clearance (diffusive, convective)	Convective clearance (*e.g.*, CVVH) is associated with somewhat greater clearance of middle molecular weight medications than diffusive clearance (*e.g.*, CVVHD).
KRT dose	Greater KRT intensity is associated with greater medication clearance. Caution should be used when extrapolating historical literature to present state where KRT doses were generally lower.
Site of replacement fluids	Administration of replacement fluids before the dialyzer (predilution) will decrease medication clearance modestly in convective clearance circuit configurations.
Circuit downtime[b]	Greater downtime is associated with reduced medication clearance. More than 4–6 h of downtime during CKRT should prompt re-evaluation of the medication dosing schema.
Dialyzer[b]	Contemporary dialyzers have improved efficiency, which may increase medication clearance compared with historical practice. Caution should be used when extrapolating historical literature with less efficient dialyzers to current state.
Patient factors	
Vascular access	KRT using an arteriovenous fistula or graft facilitates greater blood flow and medication clearance than using an acutely placed central catheter.
Residual kidney function[a]	Endogenous kidney clearance of the medication can contribute to greater total body clearance than with the extracorporeal circuit alone. Urine output >0.5 ml/kg per hour may be an indicator of clinically significant kidney clearance warranting higher medication doses.

CKRT, continuous KRT; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CL, clearance.
[a]Other relevant considerations that are somewhat less impactful clinically: (*1*) degree to which kidney clearance contributes to total body clearance of the medication (*i.e.*, Total $CL=CL_{renal}+CL_{hepatic}+CL_{extracorporeal}+CL_{other}$); (*2*) electrical charge may affect clearance depending on the composition of the dialyzer (*e.g.*, a negatively charged membrane may attract cationic molecules). Collectively, physicochemical properties of a medication are used to characterize the sieving coefficient (convective clearance) or the saturation coefficient (diffusive clearance), which may range from 0 (no passage across the semipermeable membrane) to 1 (complete passage across the semipermeable membrane).
[b]Use of guideline-directed anticoagulation during CKRT has decreased circuit downtime and improved dialyzer patency. Prolonged dialyzer lifespan may decrease medication clearance.

creatinine and cystatin C will be unreliable to estimate GFR while on KRT. Failure to account for residual kidney function would risk underdosing and subtherapeutic medication exposure. Both endogenous kidney and extracorporeal clearance must be factored into total body elimination to select an appropriate medication dose.

Clinical Application

As with many clinical decisions, medication dosing in AKI should not rely on a single data point or consideration. Potential benefits in relation to the indication and risks from excess systemic exposure should be weighed carefully. Patients with kidney dysfunction may be at a heightened risk for drug-disease interactions such as the compounded risk of sedating drugs in patients with altered mental status from uremia. Consideration of the etiology and extent of AKI is important because rapidly recovering kidney dysfunction (*e.g.*, intravascular volume depletion, uncomplicated obstructive etiology after successful intervention) may not require dose adjustment. In early AKI, when considering antibiotics with a wide therapeutic index, some have advocated for a waiting period of

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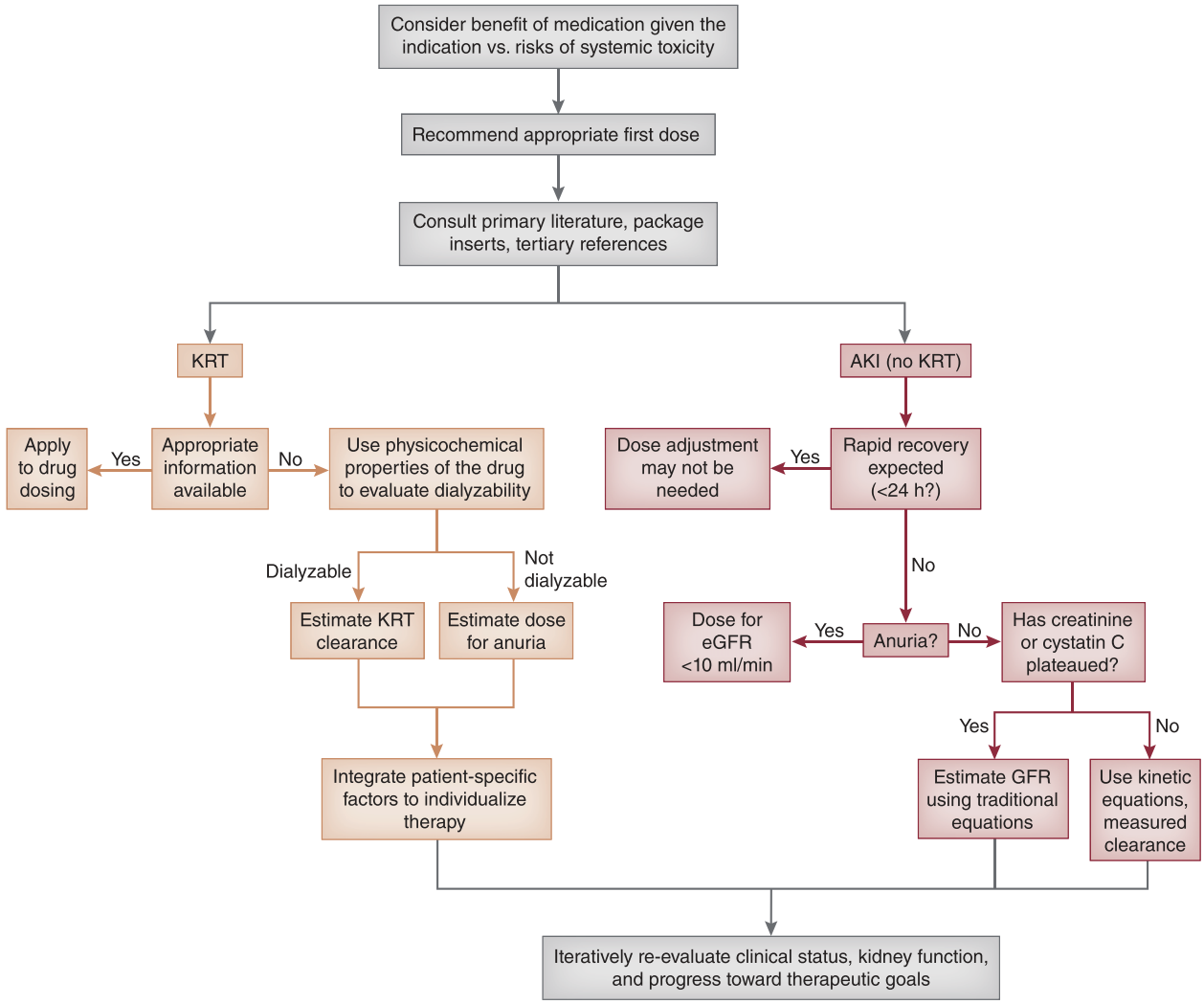

Figure 2. Approach to medication dosing in critically ill patients with AKI with or without the use of KRT. Preferred medications for use in the critically ill patient have a predictable bioavailability, fast onset, rapid titratability, and a wide therapeutic window. In patients with AKI, selection of medications should consider the benefit for the indication versus the risk of toxicity (kidney and nonkidney). The volume of distribution primarily determines the first dose of a medication, whereas clearance primarily affects the maintenance dose and interval. Given the time sensitivity of conditions in critical care (*e.g.*, sepsis, seizures, thromboembolism), the first dose of medication should therefore not be delayed on the basis of unstable kidney function or need to gather complex drug information. An appropriate, safe first dose should be administered with the consultation of a clinical pharmacist. Kidney clearance and extracorporeal clearance, if relevant, should then be estimated alongside consideration of patient-specific factors to select an individualized maintenance dosing regimen. The medication dosing and monitoring plan requires iterative re-evaluation over the arc of a patient's critical illness and kidney health.

48 hours before dose adjusting downward because many instances of community-acquired AKI rapidly recover and the potential benefit of adequate antibiotic therapy outweighs the limited risk.[47] The chronicity of a medication may also influence a clinician's approach to dosing in AKI. Owing to the increase in volume of distribution for many medications in AKI, a loading dose or increased initial dosing for a new medication may be warranted, particularly for those that are more hydrophilic; this is likely less of a consideration for a chronic maintenance medication.[47] Maintenance doses are more affected by clearance and often require a decrease in medication dose or increase in dosing interval. Deciding between these two options depends on the indication for therapy, the medication's pharmacokinetic and pharmacodynamic behavior, and the toxicity profile (Figure 2). In the critically ill patient with septic shock and AKI, for example, this might manifest as aggressive (*i.e.*, non–dose-adjusted) β-lactam dosing during the first 48 hours of therapy with a simultaneous decrease in chronic gabapentin doses. Consideration of AKI etiology and a medication's indication, chronicity, and therapeutic index are preferred to a one-size-fits-all approach for medication management in AKI.

Recommendations regarding medication dosing in KRT are available in various drug information resources; however, many extrapolate from case reports, single-dose studies performed in the outpatient setting, or from non-critically ill patients with CKD receiving KRT.[48] Therefore, these dosing recommendations poorly translate to critically

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ill patients receiving KRT because of differences in vascular access, KRT modality or dose, and underlying pharmacokinetics that are deranged in critical illness.[47] As an example, reported target attainment for antimicrobials during KRT in the critically ill ranges from 0% to 81% using standard dosing methods.[49] More aggressive dosing regimens resulted in higher target attainment of >90%.[50] Relative to the past, one must also consider that contemporary dialyzers are more efficient and flow rates are higher, both of which could increase medication clearance. Application of historical data to current practice without adjustment would increase the risk for underdosing. There is growing interest in studying the impact of KRT for new medications. For example, cefiderocol represents the first medication to include effluent rate dosing recommendations in the package insert, setting a precedent for future new drug approvals.[51]

In patients on intermittent KRT, a practical approach would be to administer cleared medications after dialysis sessions. If subtherapeutic concentrations of a narrow therapeutic window medication are expected during dialysis, an intradialytic dose could be considered, although this occurs rarely. A suggested clinical decision-making pathway regarding drug dosing in patients with AKI receiving KRT is shown in Figure 2.

The most direct measure of medication dose appropriateness in AKI is the drug concentration, detected through therapeutic drug monitoring. Therapeutic drug monitoring is particularly important for antimicrobials, antiepileptics, and medications with narrow therapeutic windows. Although the concentration of a medication in the blood may not fully reflect the concentration at the site of action, therapeutic drug monitoring can be useful to predict effectiveness and safety of medications in AKI. In patients treated with intermittent KRT, blood sampling for therapeutic drug monitoring must be spaced several hours after the dialysis session to allow for redistribution from the peripheral (tissue) to central compartment (plasma). While therapeutic drug monitoring for drugs such as vancomycin and aminoglycosides is standard, increasing literature points to benefits of therapeutic drug monitoring for most antimicrobials.[52] Assays are not available for *all* renally eliminated medications, but clinicians can use therapeutic drug monitoring results from one drug to predict the kidney clearance of another. For example, if a patient experiences unexpectedly elevated vancomycin concentrations, this should prompt re-evaluation of the dosing of other renally eliminated medications. Clinical pharmacist consultation is recommended to guide medication management in critically ill patients with AKI with and without KRT.[53]

Optimal medication management in AKI with and without KRT is a prevalent challenge for critical care clinicians. Kidney dysfunction alters medication pharmacokinetics primarily through changes to elimination and volume of distribution. Creatinine-based equations designed for unstable kidney function, novel functional biomarkers, and new real-time GFR technology may facilitate more timely and accurate dose individualization in patients with AKI. In patients with AKI requiring KRT, drug-, circuit-, and patient-specific factors each affect dose selection. Additional research is vital to identify optimal ways to individualize pharmacotherapy in critically ill patients with dynamic kidney function.

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Author Contributions

Conceptualization: Erin F. Barreto, Michael L. Behal, Alexander H. Flannery.
Writing – original draft: Michael L. Behal, Alexander H. Flannery.
Writing – review & editing: Erin F. Barreto.

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